PharmaSUG2014 - Paper DS05

Data Standards Development for Therapeutic Areas: A Focus on SDTM-Based Datasets

Fred Wood, Accenture Life Sciences, Wayne, PA
Diane Wold, Glaxo SmithKline, Research Triangle Park, NC
Rhonda Facile, CDISC, Austin, TX
Wayne Kubick, CDISC

ABSTRACT

In recent years, there has been an increasing focus on developing clinical data standards for individual therapeutic areas (TAs). A number of Therapeutic-Area User Guides (TAUGs) have been published via the collaboration of a number of standards-development organizations as well as the FDA. This presentation will provide an overview the TA development structure (CDISC, C-Path, CFAST, TransCelerate Biopharma, Inc.), the standards-development process, and some of the new SDTM (Study Data Tabulation Model)-based domains and concepts. The relationship between domains in the TAUGs and versions of the SDTMIG will also be discussed. Finally, highlights for some of the domains new to the SDTMIG (SDTM Implementation Guide) in v3.2 (e.g., Death Details, Microscopic Findings, Morphology, Procedures, and Skin Response), some of the provisional domains in TAUGs (e.g., Respiratory Measurements, Procedure Agents, and Meals), and the Disease Milestones concept will be presented.

INTRODUCTION

From its inception in 1997, CDISC has recognized the need for the establishment of standard data models to improve the process of electronic acquisition and exchange of clinical trials information for the benefit of all medical and pharmaceutical stakeholders. A number of CDISC subteams have formed since that time, each with specific goals. The CDISC Submission Data Standards (SDS) Team began its efforts in late 1999 to develop the safety domains that were defined in the now rescinded CDER 1999 Guidance. The early versions (v1.x and v2.x) were entitled "Submission Data Standards". The 3.x versions provided a standard model (the SDTM) as well as implementation advice (the SDTMIG) that could be expanded to apply to all types of clinical trial data not just safety data. For a more detailed history of the SDTM and SDTMIG through 2008, see Wood and Guinter (1).

The SDTMIG has acknowledged that sponsors will need to create "custom" domains when the modeled domains do not meet their needs, such as representing certain efficacy data for therapeutic areas, and provides advice for their creation. Each SDTMIG version issued after v3.1.1 has added new domains that the SDS Team felt would useful to most studies. Version 3.1.1 contained 24 domains, including those for relationships and trial design. By the time SDTMIG v3.2 was issued at the end of 2013, the total number of domains was 46. Despite this growth, the need for additional modeled domains is still increasing. It had been recognized that the SDS Team alone, consisting solely of volunteers, would not be able to meet the continuing demand, especially to meet the FDA's desire to have standards for therapeutic areas.

Several initiatives were begun in the second half of 2012 to advance the development of data standards for therapeutic areas (TAs). TransCelerate Biopharma, Inc. (TCB) was launched in September, with one of its initiatives being to accelerate the development of such standards through the contribution of dedicated personnel, expertise, and finances. Earlier that year, the Coalition for Accelerating Standards and Therapies (CFAST), a collaborative effort of CDISC and the Critical Path Institute (C-Path), was launched. CFAST partners included TCB, the FDA, and the NCI's Enterprise Vocabulary Services (EVS). The EVS supports all of CDISC's controlled terminology. CFAST is working to develop data standards for more than fifty-five therapeutic areas (listed on the FDA website) over the next five years, in support of the PDUFA V goals.

THERAPEUTIC-AREA STANDARDS DEVELOPMENT

CFAST HIGH-LEVEL PROCESS

CFAST has a Program Steering Committee, consisting of members from the partnering organizations, that prioritizes the TAs for which standards will be developed. The status of ongoing TA standards can be found at the CDISC website (http://www.cdisc.org/therapeutic). The grid showing the status of each TA's standards is updated approximately monthly. Data standards produced under this partnership will be created through the CDISC standards-development process, and will be published as global CDISC standards. The stages for this to happen include the following:

- Proposal Approval
- Scoping and Planning
- Concept Modeling
- Standards Development
- Internal Review
- Public Review
- Publication

PUBLISHED AND PLANNED TA STANDARDS

The published and planned therapeutic-area standards at the time of this writing are presented in the sections below.

Published

TAUG	Status	Lead Organization(s)
Alzheimer's Disease v1	Final	C-Path's Coalition Against Major Diseases
Alzheimer's Disease v2	Provisional *	CFAST (C-Path and CDISC Leads)
Asthma v1	Provisional *	CFAST (CDISC Lead)
Pain v1	Provisional *	CDISC and the Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION)
Parkinson's Disease v1	Provisional *	CDISC, National Institute of Neurological Disorders and Strokes (NINDS) and the Coalition Against Major Diseases (CAMD)
Polycystic Kidney Disease v1	Provisional *	CDISC and Critical Path Institute's Polycystic Kidney Disease Outcomes Consortium
Tuberculosis v1	Provisional *	C-Path's Critical Path to TB Drug Regimens (CPTR) and CDISC
Virology v1	Provisional *	CDISC SDS and Lab Teams
Diabetes	Public Review	CFAST (TransCelerate Lead)
Multiple Sclerosis	Public Review	C=Path

** The meaning of "provisional" is discussed in the next section.*

- **Under Development or Review**

- CV Endpoints
- Hepatitis C
- QT Studies
- Influenza
- Breast Cancer

Therapeutic Areas Approved for Development

- Major Depressive Disorder
- Rheumatoid Arthritis
- Psoriasis
- COPD
- Lipid-Lowering Agents

THE THERAPEUTIC-AREA STANDARDS-DEVELOPMENT PROCESS

The publication of the TA standards has been via the creation of TA user guides (TAUGs). For each TA (and TAUG), one or more of the standards-development organizations (CDISC, C-Path, or TCB) takes the lead. In some cases, other organizations, such as research foundations, are involved. The TAUGs provide implementation advice that supplements that in the SDTMIG. New domains developed for the TAUGs are intended to be incorporated into the SDTMIG, and some implementation advice that has broad applicability will also be incorporated into the SDTMIG. As of this writing, advice on handling situations that are specific to a particular TA will be available only in the TAUGs.

Figure 1 shows a typical development process for a new user guide. As part of the scoping process, a survey is sent out to the interested parties, for the purpose of determining how many companies are conducting research in that particular therapeutic area and what types of data they are collecting. Participants are also the asked to provide annotated CRF pages with data definitions. This information is assembled, and then composite CRF pages are created. These get mapped to CDASH domains and questions, as well as to SDTM-based domains and variables. In some cases, new SDTM variables are required. Requests for new variables are managed by the CDISC SDTM Governance Team. The end result is the creation of new proposed domains for the therapeutic area user guide, which will be classified as provisional until the new domains can be incorporated in the SDTMIG. The provisional

domains created for the therapeutic area user guide will then appear in a package for public review for the next version of the SDTMIG.

The word, “provisional”, generally applies to anything that is published (after going through all the necessary reviews) is dependent upon something else being published. For example:

- Therapeutic-Area User Guides are provisional when domains are not in an IG, or variables are not in the SDTM. The first versions of the TAUGs for Asthma and Diabetes are examples.
- Implementation guides are published as provisional when some of the domains have not yet appeared in an SDTM version. Such was the case for the first versions of the implementation guides for medical devices and associated persons.
- In general, any TAUG that depends on CT that has not yet been fully developed is also provisional.

Figure 1. Typical TA Standards-Development Process

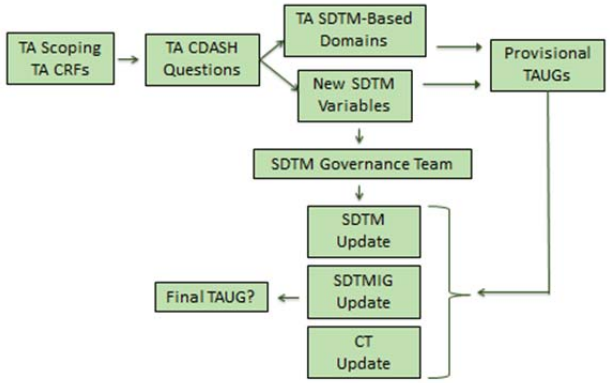

Figure 2 shows the SDTM-based domains that have been developed for various therapeutic area user guides. The first set shows those that were included in the SDTMIG v 3.2. As part of the publication process, all SDTMIG domains undergo an internal review, a review by the CDISC Standards Review Committee, and a public review before release. Following the SDMIG v3.2 domains are the domains developed for some of the newer therapeutic area user guides, which are still considered to be provisional because they have not appeared in an SDTMIG. A number of therapeutic area user guides have also made use of domains described in other implementation guides. Some of these implementation guides were not final at the time the user guides were published.

Figure 2. Domains Used in Therapeutic-Area User Guides

Therapeutic Area User Guide / Domain Source	Alzheimer's Disease v2	Asthma v1	Pain v1	Parkinson's Disease v1	Polycystic Kidney Disease v1	Tuberculosis v1	Virology v1	Diabetes
SDTMIG v3.2 New Domains								
PR - Procedures	x			x	x			
HO - Healthcare Encounters		x			x			
SR - Skin Response		x				x		
DD - Death Details					x			
MI - Microscopic Findings				x				
MO - Morphological Findings	x			x	x	x		
RP - Reproductive System Findings					x			
TAUG Provisional Domains								
BS - Bio-Specimen	x							
AG - Procedure Agents	x	x						x
NV - Nevous System Physiology	x							
RE - Respiratory System Findings		x						
UR - Urinary System Findings					x			
VR - Viral Resistance Fndings							x	
ML - Meals								x
New Concepts								
Disease Milestones Concept								x
Other Implementation Guides								
Device Domains	x	x		x	x			x
Associated Persons Domains and Concepts	x			x	x			
Pharmacogenomics Domains	x			x	x		x	

HIGHLIGHTS OF DOMAINS AND CONCEPTS DEVELOPED FOR THERAPEUTIC AREAS AND GENERAL USE, APPEARING IN SDTMIG V3.2

Death Details (DD)

This domain was developed at the request of FDA reviewers. It is based on the SEND domain, Death Diagnosis, and both are in the Findings general observation class. In SEND, this domain is limited to one record per subject (animal). In clinical use, there is no such restriction. DD allows for the submission of additional data beyond that collected in the Disposition (DS. Examples include primary cause of death, secondary cause of death, the location where the death occurred (e.g., at home or in the hospital), and whether the death was witnessed. It does not replace the need for death information in existing domains such as Adverse Events (AE), Disposition (DS), and Demographics (DM.DTHFL).

Microscopic Findings (MI)

MI is a Findings domain that had its origination in the SENDIG, and now has been modeled for clinical data. As the name implies, MI is for findings resulting from the microscopic examination of tissue samples. These examinations are performed on a specimen, which has been prepared with some type of stain. In Parkinson's disease, for example, brain tissue was examined for Alzheimer's type pathology; ischemic, hemorrhagic, or vascular pathology; and Lewy Body pathology.

The variable, --TSTDTL, is new in the SDTM v1.4, and MI is the first published domain in which it has been implemented. It is used when staining for biomarkers is examined on slides, so that specifics of the biomarker intensity could be represented, and the value in MITESTCD/MITEST could match that in other domains, such as lab tests (for which the test detail is inferred to be concentration). An example of its use is shown in the abbreviated example below.

mi.xpt

STUDYID	DOMAIN	USUBJID	MISEQ	MITESTCD	MITEST	MITSTDTL	MIORRES	MISTRESC	MIRESCAT
ABC	MI	ABC-1001	1	HER2	Human Epidermal Growth Factor Receptor 2	Reaction Score	0	0	NEGATIVE
ABC	MI	ABC-2002	1	HER2	Human Epidermal Growth Factor Receptor 2	Reaction Score	2+	2+	POSITIVE

Morphology (MO)

This Findings domain is intended for morphological changes that include macroscopic evaluations (observations made by the naked eye) and organ weights. Examples include shape, size, and color, both absolute and relative, plus any other abnormalities. MO has been used for results obtained from MRIs and Magnetic Resonance Spectroscopy for Parkinson's disease, from Optical Coherence Tomography Imaging in the Multiple Sclerosis TAUG, from CT scans in the Polycystic Kidney Disease TAUG.

Procedures (PR)

The Procedures domain belongs to the Interventions general observation class. It is designed for the submission of procedure data, regardless of whether the procedure was considered to be diagnostic or therapeutic. It would only be needed when information about the procedure such as the start time and end time are specifically collected. Examples of procedures described in the SDTMIG include disease screening, endoscopic examinations, diagnostic tests, therapeutic procedures such as cryotherapy, and surgical procedures. Measurements and evaluations obtained from procedures should be submitted in the appropriate Findings general-observation-class domain. It should be realized that many observations may have findings, and the procedure itself by which the findings were made is not considered to be important. An example would be a blood draw, which in most cases is of less interest than the results of the blood analysis, and is often implicit rather than explicit in the submitted data. If, however, the phlebotomy procedure was of interest, it would be submitted in the PR domain.

Skin Response (SR)

The Skin Response domain is the first domain using the Findings About general observation subclass that does not use an FA domain prefix. This type of implementation is new, not having been described in previous versions of the SDTMIG. It was initially developed for assessing the immunogenic potential allergen testing kits regulated by CBER, but found immediate use in the tuberculosis TAUG for reporting Mantoux test results. In the case of the allergen testing kits, a subject is often exposed to many materials at the same time. The --OBJ variable allows each specific intervention to be represented at the record level. This is illustrated in the partial example below, excerpted from the SDTMIG.

sr.xpt

STUDYID	DOMAIN	USUBJID	SRSEQ	SRTESTCD	SRTEST	SROBJ	SRORRES
CC-001	SR	CC-001-101	1	RCTGRDE	Reaction Grade	Dog Epi IgG 0 mg	NEGATIVE
CC-001	SR	CC-001-101	4	RCTGRDE	Reaction Grade	Dog Epi IgG 1 mg	ERYTHEMA, INFILTRATION, PAPULES, VESICLES
CC-001	SR	CC-001-101	6	RCTGRDE	Reaction Grade	Dog Epi IgG 2 mg	ERYTHEMA, INFILTRATION, PAPULES, COALESCING VESICLES
CC-001	SR	CC-001-101	7	WHEALDIA	Wheal Diameter	Dog Epi IgG 0 mg	5
CC-001	SR	CC-001-101	10	WHEALDIA	Wheal Diameter	Dog Epi IgG 1 mg	100
CC-001	SR	CC-001-101	12	WHEALDIA	Wheal Diameter	Dog Epi IgG 2 mg	8

HIGHLIGHTS OF DOMAINS AND CONCEPTS DEVELOPED FOR THERAPEUTIC AREAS AND GENERAL USE, PROVISIONAL DOMAINS

Respiratory Measurements, Procedure Agents, and Meals

Respiratory Measurements (RE) and Procedure Agents (AG) first appeared in Asthma TAUG. Respiratory Measurements is a Findings general observation class domain designed to include data on respiratory physiological findings. Examples include forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and peak expiratory flow. The Procedure Agents domain is also present in the Diabetes TAUG. It is an Interventions domain, created for the submission of compounds that were administered as part of a procedure. Such exposures have generally been difficult to characterize, since they are not really study treatments or concomitant medications. In asthma, it was used to submit dosing information for agents administered as part of an airway responsiveness test, as well as dosing of albuterol for reversibility.

In the Diabetes TAUG, AG was used to represent dosing information for the meal in a mixed-meal tolerance test. It would also be used for glucose administered in a glucose tolerance test. In contrast, the Meal (ML) domain, another in the Interventions general observation class, was designed to represent the ingestion of meals that were not part of any specific procedure. In the Diabetes TAUG, for example, it was used for the collection data around the last meal prior to a hypoglycemic event.

THE DISEASE MILESTONES CONCEPT

The concept of Disease Milestones arose in the context of representing information collected around a hypoglycemic event in diabetes trials. The information typically includes the following (with the domains shown in parentheses):

- Data about the event and prespecified symptoms (Clinical Events, CE)
- Blood glucose (self-monitored) at the time of the event (Labs, LB)
- Last dose of study medication (e.g., insulin or an analog) prior to the event (Exposure, EX)
- Last meal prior to the event (Meals, ML)
- Whether any hypoglycemic medications were taken after the event, along with a pre-specified list (Concomitant Medications, CM)

This data was initially modeled using time-point and reference-time-point variables. This modeling is shown in Figure 3. A larger version, with shading (and stippling) friendly to black and white printing can be found in Appendix 1. The hypoglycemic event is given the name, in this case “Hypoglycemic Event 1” which is shaded yellow in all domains. The hypoglycemic event was mapped to the --TPT variable in CE and LB. The data collected in ML, EX, and CM consider the hypoglycemic event to be a time point reference, and it appears in --TPTREF. The --TPT variable in these latter three domains reflects the time at which this information is being collected relative to the event itself. This has been shaded in blue.

There are probably a number of other mapping scenarios that could have been used for these data. For example, one might have considered the hypoglycemic event to be a time point reference (--TPTREF) in CE and LB, but --TPTREF is an anchor for time points, and there is no --TPTREF in these datasets. Regardless, there is no escaping the fact that there will be confusion between what is a time point and what is a time point reference when looking at the event, which is an anchor, and the data collected around this anchor. Other limitations include the fact that time-point variables are defined as planned, and time-point-reference variables are anchors; both are typically protocol specified. Because there is no consistent key that relates all the data collected about a hypoglycemic event, it's likely that RELREC would be needed, as shown. Add: RELREC is not without its complexities in this case. The problem is that one would not know the RELTYPE value for all of them until all the data had been collected, and it may vary from subject to subject, or by event within each subject. As a result, the example is showing some question marks.

Figure 3. Time-Point Variables and Reference Time Points

ce.xpt

STUDYI	DOMAIN	USUBJID	CESEQ	CETERM	CECAT	CEPRESP	CEOCCUR	CETPT	CESTDTC
XYZ	CE	XYZ-001-001	1	HYPOGLYCEMIA	HYPOGLYCEMIA			HYPOGLYCEMIC EVENT 1	2013-09-01T23:00
XYZ	CE	XYZ-001-001	2	SWEATING	HYPOGLYCEMIA	Y	Y	HYPOGLYCEMIC EVENT 1	

lb.xpt

STUDYI	DOMAIN	USUBJID	SPDEVID	LBSEQ	LBTESTCD	LBTEST	LBORRES	LBORRESU	LBSTRESC	LBSTRESN	LBSTRESU	LBSPE	LBDTC	LBTPT
XYZ	LB	XYZ-001-001	GLUCOMETER	1	GLUC	GLUCOSE	60	mg/dL	3.33	3.33	mmol/L	BLOOD	2013-09-01T23:10	HYPOGLYCEMIC EVENT 1

ml.xpt

STUDYID	DOMAIN	USUBJID	MLSEQ	MLTRT	MLTPT	MLTPTREF	MLRFTDTC
XYZ	ML	XYZ-001-001	1	EVENING MEAL	LAST INTERVENTION PRIOR TO	HYPOGLYCEMIC EVENT 1	2013-09-01T23:00

ex.xpt

STUDYI	DOMAIN	USUBJID	EXSEQ	EXTRT	EXCAT	EXDOSE	EXDOSU	EXSTDTC	EXTPT	EXTPTREF	EXRFTDTC
XYZ	EX	XYZ-001-001	1	DRUG A	HIGHLIGHTED DOSE	10	mg	2013-09-01T019:00	LAST INTERVENTION PRIOR TO	HYPOGLYCEMIC EVENT 1	2013-09-01T23:00

cm.xpt

STUDYI	DOMAIN	USUBJID	CMSEQ	CMTRT	CMCAT	CMSCAT	CMPRESP	CMOCCUR	CMTPT	CMTPTREF
XYZ	CM	XYZ-001-001	1	Hypoglycemia treatments	HYPOGLYCEMIC TREATMENTS		Y	Y	IMMEDIATELY AFTER THE EVENT	HYPOGLYCEMIC EVENT 1
XYZ	CM	XYZ-001-001	4	Glucose tablets	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	Y	IMMEDIATELY AFTER THE EVENT	HYPOGLYCEMIC EVENT 1
XYZ	CM	XYZ-001-001	5	Glucagon Injection	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	N	IMMEDIATELY AFTER THE EVENT	HYPOGLYCEMIC EVENT 1
XYZ	CM	XYZ-001-001	6	Intravenous glucose	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	N	IMMEDIATELY AFTER THE EVENT	HYPOGLYCEMIC EVENT 1

relrec.xpt

STUDYI	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
XYZ	CE		CETPT		MANY	A
XYZ	LB		LBTPT		MANY	A
XYZ	ML		MLTPTREF		ONE	A
XYZ	EX		EXTPTREF		?	A
XYZ	EX		CMTPTREF		?	A

As a result of the challenges using the time-point and time-point-reference variables, another approach has been proposed. Input on this approach has been requested during the Public Comment period of the Diabetes TAUG, which was posted on April 11th. At the time of its development, the Disease Milestones approach was envisioned to be applicable to other situations as well. Thus, it was given the relatively generic name of Disease Milestones. The mapping of the data for this approach is shown in Figure 4. A larger version, with shading (and stippling friendly to black and white printing) can be found in Appendix 1. In this model, everything is based upon the following

- A reference event, referred to as a disease milestone (MIDS, shaded in yellow)
- The relationship of other observations relative to that event (MIDSREL, shaded in blue).

Figure 4. Disease Milestones Concept

ce.xpt

STUDYI	DOMAI	USUBJID	CESEQ	CETERM	CECAT	CEPRESP	CEOCCUR	MIDS	MIDSREL	MIDSDTC	CESTDTC
XYZ	CE	XYZ-001-001	1	HYPOGLYCEMIA	HYPOGLYCEMIA			HYPOGLYCEMIC EVENT 1		2013-09-01T11:00	2013-09-01T23:00
XYZ	CE	XYZ-001-001	2	SWEATING	HYPOGLYCEMIA	Y	Y	HYPOGLYCEMIC EVENT 1	DURING	2013-09-01T11:00	

lb.xpt

STUDYID	DOMAIN	USUBJID	SPDEVID	LBSEQ	LBTESTCD	LBTEST	LBORRES	LBORRESU	LBSTRESC	LBSTRESN	LBSTRESU	LBSPEC	LBDTC	MIDS	MIDSREL
XYZ	LB	XYZ-001-001	GLUCOMETER	1	GLUC	GLUCOSE	60	mg/dL	3.33	3.33	mmol/L	BLOOD	2013-09-01T23:10	HYPOGLYCEMIC EVENT 1	DURING

ml.xpt

STUDYI	DOMAI	USUBJID	MLSEQ	MLTRT	MIDS	MIDSREL	MLRFTDTC
XYZ	ML	XYZ-001-001	1	EVENING MEAL	HYPOGLYCEMIC EVENT 1	LAST INTERVENTION PRIOR TO	2013-09-01T23:00

ex.xpt

STUDYI	DOMAI	USUBJID	EXSEQ	EXTRT	EXCAT	EXDOSE	EXDOSU	EXSTDTC	MIDS	MIDSREL	EXRFTDTC
XYZ	EX	XYZ-001-001	1	DRUG A	HIGHLIGHTED DOSE	10	mg	2013-09-01T019:00	HYPOGLYCEMIC EVENT 1	LAST INTERVENTION PRIOR TO	2013-09-01T23:00

cm.xpt

STUDYI	DOMAI	USUBJID	CMSEQ	CMTRT	CMCAT	CMSCAT	CMPRESP	CMOCCUR	MIDS	MIDSREL
XYZ	CM	XYZ-001-001	1	HYPOGLYCEMIC TREATMENTS	HYPOGLYCEMIC TREATMENTS		Y	Y	HYPOGLYCEMIC EVENT 1	IMMEDIATLEY AFTER THE EVENT
XYZ	CM	XYZ-001-001	4	GLUCOSE TABLETS	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	Y	HYPOGLYCEMIC EVENT 1	IMMEDIATLEY AFTER THE EVENT
XYZ	CM	XYZ-001-001	5	GLUCAGON INJECTION	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	N	HYPOGLYCEMIC EVENT 1	IMMEDIATLEY AFTER THE EVENT
XYZ	CM	XYZ-001-001	6	INTRAVENOUS GLUCOSE	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	N	HYPOGLYCEMIC EVENT 1	IMMEDIATLEY AFTER THE EVENT

This mapping is consistent across all domains collecting data for the hypoglycemic event, as shown by the yellow and blue shading. Because of this consistency, RELREC is not needed.

Another part of the Disease Milestone concept is the idea that these can be defined at the trial level, as shown in the following table. The last column, MIDSRPT, indicates whether the Milestone repeats.

Prototype Trial Milestones (tm.xpt)

STUDYID	DOMAIN	TMSEQ	MIDS	MIDSDEF	MIDSRPT
ABC	TM	1	HYPOGLYCEMIC EVENT	Hypoglycemic Event, the occurrence of a blood glucose concentration below the specified (by study) level of hypoglycemia	Y

In much in the same way that the Trial Elements and Trial Visits have corresponding subject-level domains, Trial Milestones has a corresponding subject-level domain, Subject Milestones, shown below. Although the focus in this section has been on a single hypoglycemic event, the subject milestones table will contain a record for every hypoglycemic event experienced by the subject in the trial. For illustrative purposes, the subject milestones table below shows that the subject had two hypoglycemic events.

Prototype Subject Milestones (sm.xpt)

STUDYID	DOMAIN	USUBJID	SMSEQ	MIDS	SMSTDTC	SMSTDY	SMENDTC	SMENDY
ABC	SM	ABC-1001	2	HYPOGLYCEMIC EVENT 1	2013-09-01T11:00	25	2013-09-01T11:00	25
ABC	SM	ABC-1001	3	HYPOGLYCEMIC EVENT 2	2013-09-24T08:48	50	2013-09-24T08:48	50

CONCLUSIONS

Standards initiatives such as CFAST and those supported by TransCelerate have had a significant impact on rate of standards development. The combination of dedicated resources provided by TransCelerate member companies, the volunteer membership of CDISC teams, and the FDA's support of CDISC standards, has resulted in the availability of standards for widespread use at a greater rate than had been previously possible. This is evidenced by the fact that almost all the new domains in SDTMIG v3.2 are the result of standards development for therapeutic areas. These collaborative efforts of industry clinical experts and data-standards experts have also resulted in a number of new examples for already existing SDTMIG domains. It is expected that the development of new domains for future versions of the SDTMIG will follow this trend.

REFERENCES

1. Wood, F., and Guinter, T. (2008) Evolution and Implementation of the CDISC Study Data Tabulation Model (SDTM). Pharmaceutical Programming 1 (1): 20-27.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the lead author at:

Name: Fred Wood
Enterprise: Accenture Life Sciences, Accelerated R&D Services
Work Phone: 484-881-2297
E-mail: f.wood@accenture.com

Appendix 1 (Page 1)
Time Point and Reference Time Points vs. Disease Milestones for Hypoglycemic Events (Page 1 of 2)

Time-Point and Reference Time Point Approach*

ce.xpt

STUDYID	DOMAIN	USUBJID	CESEQ	CETERM	CECAT	CEPRESP	CEOCCUR	CETPT	CESTDTC
ABC	CE	ABC-1001	1	HYPOGLYCEMIA	HYPOGLYCEMIA			HYPOGLYCEMIC EVENT 1	2013-09-01T11:00
ABC	CE	ABC-1001	2	SWEATING	HYPOGLYCEMIA	Y	Y	HYPOGLYCEMIC EVENT 1	

lb.xpt

STUDYID	DOMAIN	USUBJID	SPDEVID	LBSEQ	LBTESTCD	LBTEST	LBORRES	LBORRESU	LBSTRESC	LBSTRESN	LBSTRESU	LBSPEC	LBDTC	LBTPT
ABC	LB	ABC-1001	GLUCOMETER	1	GLUC	GLUCOSE	60	mg/dL	3.33	3.33	mmol/L	BLOOD	2013-09-01T11:00	HYPOGLYCEMIC EVENT 1

ml.xpt

STUDYID	DOMAIN	USUBJID	MLSEQ	MLTRT	MLTPT	MLTPTREF	MLRFTDTC
XYZ	ML	XYZ-001-001	1	EVENING MEAL	LAST INTERVENTION PRIOR TO	HYPOGLYCEMIC EVENT 1	2013-09-01T11:00

ex.xpt

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXCAT	EXDOSE	EXDOSU	EXSTDTC	EXTPT	EXTPTREF	EXRFTDTC
ABC	EX	ABC-1001	1	DRUG A	HIGHLIGHTED DOSE	10	mg	2013-09-01T07:00	LAST INTERVENTION PRIOR TO	HYPOGLYCEMIC EVENT 1	2013-09-01T11:00

cm.xpt

STUDYID	DOMAIN	USUBJID	CMSEQ	CMTRT	CMCAT	CMSCAT	CMPRESP	CMOCCUR	CMTPT	CMTPTREF
ABC	CM	ABC-1001	1	Hypoglycemia treatments	HYPOGLYCEMIC TREATMENTS		Y	Y	IMMEDIATLEY AFTER THE EVENT	HYPOGLYCEMIC EVENT 1
ABC	CM	ABC-1001	4	Glucose tablets	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	Y	IMMEDIATLEY AFTER THE EVENT	HYPOGLYCEMIC EVENT 1
ABC	CM	ABC-1001	5	Glucagon Injection	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	N	IMMEDIATLEY AFTER THE EVENT	HYPOGLYCEMIC EVENT 1
ABC	CM	ABC-1001	6	Intravenous glucose	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	N	IMMEDIATLEY AFTER THE EVENT	HYPOGLYCEMIC EVENT 1

** The shading shows hypoglycemic events with horizontal stippling and the timing relative to the events with vertical stippling.*

Appendix 1 (Page 2)
Time Point and Reference Time Points vs. Disease Milestones for Hypoglycemic Events (Page 2 of 2)

Time-Point and Reference Time Point Approach*

relrec.xpt

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
XYZ	CE		CETPT		MANY	A
XYZ	LB		LBTPT		MANY	A
XYZ	ML		MLTPTREF		ONE	A
XYZ	EX		EXTPTREF		?	A
XYZ	EX		CMTPTREF		?	A

Appendix 1 (Page 3)
Time Point and Reference Time Points vs. Disease Milestones for Hypoglycemic Events

Disease Milestones Concept*

ce.xpt

STUDYID	DOMAIN	USUBJID	CESEQ	CETERM	CECAT	CEPRESP	CEOCCUR	MIDS	MIDSREL	MIDSDTC	CESTDTC
ABC	CE	ABC-1001	1	HYPOGLYCEMIA	HYPOGLYCEMIA			HYPOGLYCEMIC EVENT 1		2013-09-01T11:00	2013-09-01T11:00
ABC	CE	ABC-1001	2	SWEATING	HYPOGLYCEMIA	Y	Y	HYPOGLYCEMIC EVENT 1	DURING	2013-09-01T11:00	

lb.xpt

STUDYID	DOMAIN	USUBJID	SPDEVID	LBSEQ	LBTESTCD	LBTEST	LBORRES	LBORRESU	LBSTRESC	LBSTRESN	LBSTRESU	LBSPEC	LBDTC	MIDS	MIDSREL
ABC	LB	ABC-1001	GLUCOMETER	1	GLUC	GLUCOSE	60	mg/dL	3.33	3.33	mmol/L	BLOOD	2013-09-01T11:00	HYPOGLYCEMIC EVENT 1	DURING

ml.xpt

C	DOMAIN	USUBJID	MLSEQ	MLTRT	MIDS	MIDSREL	MLRFTDTC
ABC	ML	ABC-1001	1	EVENING MEAL	HYPOGLYCEMIC EVENT 1	LAST INTERVENTION PRIOR TO	2013-09-01T11:00

ex.xpt

STUDYID	DOMAIN	USUBJID	EXSEQ	EXTRT	EXCAT	EXDOSE	EXDOSU	EXSTDTC	MIDS	MIDSREL	EXRFTDTC
ABC	EX	ABC-1001	1	DRUG A	HIGHLIGHTED DOSE	10	mg	2013-09-01T07:00	HYPOGLYCEMIC EVENT 1	LAST INTERVENTION PRIOR TO	2013-09-01T11:00

cm.xpt

STUDYID	DOMAIN	USUBJID	CMSEQ	CMTRT	CMCAT	CMSCAT	CMPRESP	CMOCCUR	MIDS	MIDSREL
ABC	CM	ABC-1001	1	HYPOGLYCEMIC TREATMENTS	HYPOGLYCEMIC TREATMENTS		Y	Y	HYPOGLYCEMIC EVENT 1	IMMEDIATLEY AFTER THE EVENT
ABC	CM	ABC-1001	4	GLUCOSE TABLETS	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	Y	HYPOGLYCEMIC EVENT 4	IMMEDIATLEY AFTER THE EVENT
ABC	CM	ABC-1001	5	GLUCAGON INJECTION	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	N	HYPOGLYCEMIC EVENT 5	IMMEDIATLEY AFTER THE EVENT
ABC	CM	ABC-1001	6	INTRAVENOUS GLUCOSE	HYPOGLYCEMIC TREATMENTS	MEDICATION	Y	N	HYPOGLYCEMIC EVENT 6	IMMEDIATLEY AFTER THE EVENT

** The shading shows hypoglycemic events with horizontal stippling and the timing relative to the events with vertical stippling.*